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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,356	01/26/2005	Christopher Bruce Alexander Whitelaw	102286.155US1	1380

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WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
12/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
sharon.matthews@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,356	WHITELAW ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-35* is/are pending in the application.

4a) Of the above claim(s) *29,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-3-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of species A, induction of a toxicological stress, in the reply filed on 11-21-07 is acknowledged. The traversal is on the ground(s) that the special technical feature of the pending claims is a novel method for detecting gene activation events, which defines a contribution over the prior art. The reporter gene in the pending claims indicates the initiation of gene transcription event whose occurrence is predictive of the subject test animal developing a condition of species A-D, and there is no undue burden for Examiner to search different gene activation events. This is not found persuasive because the putative special technical feature of species A-D is the transgenic non-human animal that comprises a construct expressing a member of the lipocalin family, such as beta-lactoglobulin (BLG), rather than the method claims of claims 33-35. Since the art of record teaches generation of transgenic mice comprising genomic constructs expressing the ovine beta-lactoglobulin, therefore, no special technical feature is contributed over the prior art by the instant invention. Further, technical features of each gene activation events of induction of toxicological stress, metabolic changes, disease results from viral, bacterial, fungal or parasitic infection, and cancer, inflammatory disease, neurological disease and disease with a genetic basis are distinguished from each other. The transgenic animal expressing BLG could be used in a method to detect any of the distinctive species of gene activation and would not overlap with other species of gene activation. The search for each species would not be coextensive and they require separate search. Thus, there would be serious burden for Examiner to search all species A-D.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 34 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11-21-07.

Applicants' preliminary amendments filed on 1-26-05 and 10-24-05 have been entered. Claims 1-21 have been canceled. Claims 22-35 have been added. Claim 27 has been amended. Claims 22-35 are pending. It is noted that Applicants elected beta-lactoglobulin as lipocalin species, epitope species of SEQ ID No. 1, which is EQKLISEEDL from c-myc, and promoter element Cyp1a1 in the response filed on 5-29-07. Since the elected Cyp1a1 promoter element is not recited in claim 29, therefore, claim 29 will NOT be considered. Claims 29, 34 and 35 are not considered. Claims 22-28 and 30-33, and a method of detecting or screening gene activation event of toxicologically induced stress by using a transgenic non-human animal expressing a peptide-tagged lipocalin reporter, are under consideration.

Specification

3. The disclosure is objected to because of the following informalities: The term "CLAIMS" on page 50 of the specification is improper. Changing the term "CLAIMS" to "We claim:" or "What is claimed is:" would be remedial.

Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequences in Figures 7-9, 15 and 18-23 or in the

"BRIEF DESCRIPTION OF THE DRAWINGS". Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequences on pages 11, 12, 38, 44 and 45 of the specification. Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required.

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example, pages 8 and 16. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 25, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "a stress inducible promoter operatively isolated from a nucleic acid sequence encoding a member of the lipocalin protein family by a nucleotide sequence flanked by nucleic acid sequences recognized by a site specific recombinase" in claim 30 is vague and renders the claim indefinite. It is unclear what is intended to claim. It is unclear what the phrase

"operatively isolated" means and how a promoter "operatively isolated" from a nucleic acid sequence. It is unclear what the sentence "a member of the lipocalin protein family **by a nucleotide sequence** flanked by nucleic acid sequences recognized by a site specific recombinase" means. It is unclear how a member of the lipocalin protein family "by a nucleotide sequence". Claim 31 depends from claim 30.

The phrase "accession No. X12817" in claim 25 is vague and render the claim indefinite. It is unclear from what database the "accession No. X12817" comes from. Further, the sequence in an accession No. of a database keep changing because of different revision of the sequence, therefore, it is unclear exactly what sequence is represented in an accession No.

7. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The omitted steps are: How the transgenic non-human animal is screened, what agent is used, how to induce stress, what is screened, and how to determine the toxicologically induced stress occurs.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 22-28 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on transgenic non-human animal and its use for detecting and screening a gene activation event of toxicologically induced stress. The claims encompass the use of tens of thousands of numerous different transgenic non-human animals, such as mice, rats, rabbits, cows, goats, sheep, monkeys, whales, other mammals, birds, fishes, insects etc., comprising a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of Cyp1a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID No. 1, and having various unknown and unidentified phenotypes. The specification fails to disclose any transgenic non-human animal having any particular phenotype and said transgenic non-human animal can be used for detecting and screening the claimed gene activation event. The specification fails to disclose the structural feature or phenotype of the claimed various transgenic non-human animals. The structural features and phenotypes of the transgenic non-human animals that can distinguish said transgenic non-human animals from wild-type animals have not been disclosed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed transgenic non-human animals, and because the claimed transgenic non-human animals are highly variant, the information as disclosed in the present application is insufficient to describe the claimed transgenic non-human animals and their uses.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed transgenic non-human animals. Thus, it is

concluded that the written description requirement is not satisfied for the transgenic non-human animals and their uses as claimed.

10. Claims 22-28 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are drawn to a method of detecting a gene activation event in vivo by assaying a transgenic non-human animal whose cells express a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of Cyp1a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID No. 1, wherein the animal is subjected to a gene activation event of toxicologically induced stress, and a method of screening for, or monitoring of toxicologically induced stress by using said transgenic non-human animal.

The claims read on transgenic non-human animal and its use for detecting and screening a gene activation event of toxicologically induced stress. The claims encompass the use of tens of thousands of numerous different transgenic non-human animals, such as mice, rats, rabbits, cows, goats, sheep, monkeys, whales, other mammals, birds, fishes, insects etc., comprising a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of Cyp1a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID No. 1, and having various unknown and unidentified phenotypes.

The specification only discuss using one of several standard methods including pronuclear injection, blastocyst injection of transfected cells or using viral vector to generate transgenic animals. Preparation of vector pXC3'mycBLG and the use of said vector to produce transgenic animals (Example 11, p. 48-49). The specification fails to generate any transgenic animals. The specification fails to provide adequate guidance and evidence for what would be the phenotype of the transgenic animals and whether said transgenic animals can be used for detecting and screening gene activation event of toxicologically induced stress as claimed.

The claims encompass using numerous different transgenic non-human animals to detect and screen toxicologically induced stress in vivo. Applicants do NOT have possession of any transgenic non-human animal, therefore, one skilled in the art at the time of the invention would not know how to use various transgenic non-human animals for the claimed method. Further, the state of the art of transgenics at the time of the invention held that the phenotype of transgenic animals was unpredictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Wall, R. J., 1996 (Theriogenology, Vol. 45, p. 45-68) states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (e.g. p. 61, last paragraph), and "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies" (e.g. p. 62, first paragraph). In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that "animal transgenics is still suffering from technical limitations" (e.g. abstract).

Further, the genetic background of the transgenic animal has a large impact on the resulting phenotype of the transgenic animal. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing

the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

The claims encompass using different beta-lactoglobulin derived from various organisms. Different beta-lactoglobulin proteins have different amino acid sequences. The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further

states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, the biological function of protein was unpredictable at the time of the invention and different beta-lactoglobulin could have different biological functions, which adds to the unpredictable resulting phenotype of the transgenic non-human animals expressing various beta-lactoglobulin proteins.

Since resulting phenotype of the transgenic non-human animals expressing the claimed construct was unpredictable at the time of the invention, one skilled in the art at the time of the invention would not know whether the claimed transgenic non-human animals would have any phenotype and whether the phenotype, if any, would be distinguishable from the wild type animals, and whether said transgenic non-human animals could be used for detecting and screening the gene activation event of toxicologically induced stress. In addition, the claims fail to recite how to induce stress, what agent or method is used to induce stress, what is screened, and how to determine the toxicologically induced stress occurs. Absent specific guidance and evidence, one skilled in the art at the time of the invention would not know how to use the claimed transgenic non-human animals for detecting and screening the gene activation event of toxicologically induced stress as claimed.

The specification contemplates using blastocyst injection of transfected cells to generate transgenic non-human animals. Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more

frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column). It appears only two mouse ES cell lines can be used to generate transgenic mice and no other known ES cell lines have been established to generate any other transgenic animals.

In view of the lack of ES cells other than the mouse ES cells for making transgenic animals, the inherent unpredictability of the resulting phenotypes of various transgenic non-human animals comprising the claimed construct and the influence of the genetic backgrounds of different animals on the resulting phenotype, one skilled in the art at the time of the invention would not know how to make and/or use the transgenic non-human animals having the claimed construct and exhibiting various unknown and unidentified phenotypes, and how to use said transgenic non-human animals for detecting and screening gene activation event of toxicologically induced stress.

The breadth of claims also encompasses chimeric animal containing cells comprising the claimed construct. The specification fails to enable making chimeric animals such that they exhibit expression of the claimed construct. The specification does not correlate chimeric animal, comprising cells with the claimed construct to any phenotype. The method of making

genetic mosaic animal is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animals is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Kappel; Sigmund) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric animals encompassed by the claims is highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric animal exhibiting any specific phenotype or any phenotype other than wild type. As set forth above, without a predictable phenotype, it would require additional and undue experimentation for one of skill in the art at the time of the invention to determine the use of a chimeric animal comprising the claimed construct.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of the experimentation required and the breadth of the claims that it would require undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.